Bovine-derived Products Used in the Manufacture and Formulation of Vaccines: Current Policies and Issues for the Future

William M. Egan, Ph.D.
Acting Director
Office of Vaccines Research and Review

September, 2004 – FDA/PDA Meeting

Examples of Bovine-derived Products Used in Vaccine Manufacture

- Fetal calf serum
- Beef muscle/organ extracts
- Gelatin/processed gelatin
- Small molecules (amino acids, peptides, lactose, Tween, glycerol)

CBER's Policy Regarding the Sourcing of Bovine-derived Materials

"[T]hat manufacturers ... assure that materials derived from all species of ruminant animals born, raised, or slaughtered in countries where BSE is known to exist, or countries where the USDA has been unable to assure FDA that BSE does not exist, are not used in the manufacture of FDA-regulated products intended for administration to humans."

[April, 2000, CBER Letter to Manufacturers of Biological Products]

CBER's Policy Regarding the Sourcing of Bovine-derived Materials

- May, 1991, CBER Letter to Manufacturers
- December, 1993, FDA Letter to Manufacturers
- May, 1996, FDA Letter to Manufacturers
- September, 1997, FDA Guidance for Industry on the Sourcing and Processing of Gelatin
- April, 2000, CBER Letter to Manufacturers of Biological Products
- May, 1993, Points to Consider in the Characterization of Cell Lines used to produce Biologics. (This guidance document is being updated)

Vaccines not Following CBER/FDA Recommendations

- In early 2000, through a product review, CBER learned that its recommendations were not universally followed for all vaccines.
- Risk estimates for various situations were carried out and CBER developed recommendations for the affected manufacturers.
- Discussed in a joint session of the TSE Advisory Committee and Vaccines and Related Products Advisory Committee (7/2000).

Recommendations of the July, 2000 Joint Advisory Committees

- Bovine-derived materials used in the routine production of vaccines that are sourced from countries on the USDA list should be replaced with bovine-derived materials from countries not on the USDA list
- Working bacterial and viral seed banks and WCBs that were established with bovine-derived material from countries on the USDA list should be re-derived with bovine-derived materials from countries not on the USDA list

Recommendations of the Joint Advisory Committees (cont'd)

- Master viral and bacterial seed banks that were established with bovine-derived material from countries on the USDA list need not be re-derived with bovine-derived materials from countries not on the USDA list.
- These issues are of public interest and the public should be informed about the safety of vaccines that used materials from countries on the USDA list and the assessment of the nature of any risk for vCJD from such vaccines.

Update from 2000 Meeting

- Web site created containing transcript of AC meeting, risk assessments, and listing of affected vaccines with periodic updates; **www.fda.gov/cber/bse/bse.htm**.
- New sources of bovine materials found and used in manufacturing.
- Working cell and seed banks re-derived, qualified, and placed into production.
- Nearly all of the affected vaccines are now out of date

The Policy is Clear, But ...

Source country control can be problematic when new countries are added to the list:

- Licensed products remain on the market
- Manufacturing time-lines are long (> 1 year)
- The status of master cell and seed banks, as well as working cell and seed banks, become unclear; re-derivation and re-qualification take time and may not always be possible
- The status of products in development (pre-IND through BLA) becomes unclear
- Risk – benefit decisions continue to be needed

EMEA Guidance on Minimizing the Risk of Transmitting Animal TSE Agents via Medicinal Products

- Revision of 1/28/04; date of application of the note is July 1, 2004
- Undertaken to introduce, *inter alia*, risk assessment into the regulatory compliance process, clarify terms and classifications, and take into account advances in scientific knowledge
- Use of the revised WHO infectivity classification scheme
- Guidance applied prospectively

Vaccines and North American Sourced Bovine Materials

- BSE-infected cows found in Canada and the U.S., the latter being born in Canada
- Bovine-derived materials from cattle that are “born, raised, or slaughtered” in the U.S. and Canada are used in U.S.-licensed vaccines and vaccines under development.
- OVRR has not requested that vaccine manufacturers replace existing Canadian or U.S. sources of bovine-derived material.

USDA Proposed Rule re: Canada

- USDA proposed rule [October 31, 2003; http://www.aphis.usda.gov] to allow for, *inter alia*, import of:
  - Bovine animals less than 30 months of age for immediate slaughter
  - Fresh meat from carcasses of bovines less than 30 months of age; specified organs/tissues
- USDA will review comments as it makes any final decision on the importation of certain live ruminants and ruminant products from Canada and other minimal risk regions for BSE.

FDA Interim Final Rule (IFR): Use of Materials Derived from Cattle in Human Food (including dietary supplements) and Cosmetics

- July 14, 2004 [Federal Register Volume 69, Number 134; pages 42255 - 42274
- Interim final rule in response to finding of an adult cow, in the State of Washington, imported from Canada, that tested positive for BSE
- Prohibited materials are defined
- Consistent with recent USDA IFR
- FDA is currently considering changes to the ruminant feed ban regulation

US FDA Interim Final Rule: Use of Materials Derived from Cattle in Human Food (including dietary supplements) and Cosmetics

- Prohibited cattle material mean specified risk materials (SRMs), small intestine of all cattle, material from nonambulatory disabled cattle, material from cattle not inspected and passed, or MS (beef).
- SRMs mean brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (with certain exclusions), and dorsal root ganglia of cattle 30 months of age and older and the tonsils and distal ileum of the small intestine of all cattle.

Medicinal Products

A rule for medicinal products (human drugs, biologics, and medical devices, as well as veterinary drugs) is currently being developed by FDA.

Areas for Consideration

- Replacement of animal-derived materials with non-animal-derived or synthetic materials
- Use of serum-free cell culture systems
- Use of closed herds as a source of bovine materials, especially for higher risk materials, when such materials are needed.
- Replacement of human serum albumin with recombinant albumin

Areas for Potential Research

- Ability of cells (CHO cells, Vero cells, MRC-5 or WI-38 cell, etc.) to propagate the BSE agent, if present [see, e.g., I. Vorberg, A. Raines, B. Story, and S. A. Priola, "Susceptibility of common fibroblast cell lines to TSE agents," *J. Infect. Dis.*, **189**, 431-9 (2004)]
- Ability of various manufacturing steps to clear the BSE agent, if present